

compositions for use of the same purpose to form a third composition to be used for the same purpose (citing MPEP 2144.06). The Office action also asserts it would be obvious to substitute the material used for certain layers of a film tube of Okuda et al. comprising 33% PS and 67% S-Bu having a melt index of 0.5 to 10 for the material of the sidewalls and tube of the centrifugal tube of JP '190. Blackwelder is provided for teaching a blend of polystyrene having a melt flow index of around 8-10 g/10 min and a styrene butadiene block copolymer for a film tube. The Office action also asserts Blackwelder further teaches the use of polystyrene having a melt flow index of around 8-10 g/10 min would reduce hazing and hence improve clarity of the product (citing col. 4, ln. 50-52).

This rejection is respectfully traversed.

A. It is improper to combine the cited references

Claim 1 recites the sidewalls and closed end of its medical tube comprise a blend of 25-35 weight percent polystyrene, based upon total weight of the polymer, having a melt flow index of 7-11 g/10 min and a styrene-butadiene rubber block copolymer having a melt flow index of 10-12 g/10 min. There is no teaching in JP '190 to use a shrink wrap label and no teaching in Blackwelder and Okuda et al. to put their shrink wrap labels on a medical tube or to put a closed end on their shrink wrap labels.

Okuda et al. discloses the relied upon material is used for "heat shrinkable films for labeling." (Okuda et al., col. 1, lines 40-42). Blackwelder also discloses the relied upon material is used for shrinkable film for labeling. Neither Okuda et al. nor Blackwelder teach a use for their respective relied upon materials prior to orienting (stretching). It would defeat the purpose of Okuda et al. and Blackwelder to stop the handling of their respective materials prior to

orienting (stretching). Thus, it is improper to combine JP '190 and Okuda et al. or Blackwelder.

Moreover, JP '190 would not select material which heat shrinks for its tube sidewalls and closed end. Heat shrinking is not a desired property for a centrifugal tube material.

It is respectfully submitted the claimed sidewalls and closed end of the medical tube are the main body of the tube. Labeling of Okuda et al. nor Blackwelder, even if placed on tube sidewalls, is not part of the tube sidewalls.

B. There is no motivation to substitute the secondary reference materials into JP '190

The Office action asserts the impact resistance motivation disclosed for the relied upon material of Okuda et al. suffices as a reason to substitute it for the material of JP '190. However, Applicant respectfully submits this is for Okuda et al. film material that has been oriented (stretched) and then heat shrunk. There is no indication the benefit would apply to the material in its raw state and having a completely different use as the present sidewalls and end for a medical tube which are much thicker than the Okuda et al. film. Also, Okuda et al. uses the relied upon material as a film of a film, namely as layers A and C with a core layer B of different material sandwiched in between layers A and C. Okuda et al. does not teach the relied upon material has any use when used without core layer B. Thus, the motivation of Okuda et al. to use a 33% PS and 67% S-Bu copolymer is irrelevant to selecting structural material for sidewalls and end walls of the centrifugal tubes of JP '190.

C. Data shows the present invention has unexpected advantages

The present application contains data showing medical tubes made of a blend of PS has unexpected results over S-Bu tubes having 0% PS. This is particularly relevant to Claims 6, 7, 9 and 10.

The Office action asserts Okuda et al. discloses a 33% PS material. However, it is respectfully submitted it is not necessary to provide evidence comparing to the 33% PS material. The only requirement is to compare to the closest prior art. An affidavit or declaration under 37 CFR 1.132 must compare the claimed subject matter with the closest prior art to be effective to rebut a prima facie case of obviousness. MPEP 716.02(e)(ATTACHMENT I). This requirement also applies to data relied upon from the specification. “A comparison of the *claimed* invention with the disclosure of each cited reference to determine the number of claim limitations in common with each reference, bearing in mind the relative importance of particular limitations, will usually yield the closest single prior art reference.” MPEP 716.02(e) quoting *In re Merchant*, 575 F.2d 865, 868, 197 USPQ 785, 787 (CCPA 1978)(emphasis in original). The closest prior art are the S-Bu-containing tubes of JP ‘190 having 0% PS. JP ‘190 discloses tubes containing S-Bu or PS. JP ‘190 is the closest reference because it is the only reference that describes material for the sidewalls and closed end of medical tubes. The thin material for labels of Blackwelder and Okuda et al would be too flimsy to function as sidewalls and closed end of a medical tube. Moreover, the film materials of Blackwelder and Okuda et al. are not even formed into a closed end and, if they were, they would be more like a bag than a medical tube.

It is improper to require Applicants to combine teachings of different references to create new prior art to compare against.

“Although evidence of unexpected results must compare the claimed invention with the closest prior art, applicant is not required to compare the claimed invention with subject matter that does not exist in the prior art. *In re Geiger*, 815 F.2d 686, 689, 2 USPQ2d 1276, 1279 (Fed. Cir. 1987)(Newman, J.,

concurring)(Evidence rebutted *prima facie* case by comparing claimed invention with the most relevant prior art. Note that the majority held the Office failed to establish a *prima facie* case of obviousness.); *In re Chapman*, 357 F.2d 418, 148 USPQ 771 (CCPA 1966)(Requiring applicant to compare claimed invention with polymer suggested by the combination of references relied upon in the rejection of the claimed invention under 35 U.S.C. 103 ‘would be requiring comparison of the results of the invention with the results of the invention.’ 357 F.2d at 422, 148 USPQ at 714.).”

MPEP 716.02(e)(III).

The data at page 5 of the present application shows twice as many aged S-Bu tubes having 0% PS leaked as did tubes made of a blend of 30% PS/70% S-Bu polymers. This is the opposite of what was expected. As explained at page 1 of the specification, larger tubes are conventionally made of S-Bu because PS tubes shatter easily due to brittleness. Thus, it is unexpected to reduce brittleness by adding PS (the conventionally thought to be *more brittle* material) to S-Bu (the conventionally thought to be *less brittle* material).

Example 2 of the specification tests resistance to plastic deformation of PS and S-Bu blends compared to S-Bu tubes having 0% PS. The table at page 6 shows the 25 and 30% PS blends are surprisingly comparable to pure S-Bu. In particular, the data at pages 6 and 7 shows an advantage over S-Bu tubes having 0% PS in tests at 3500 rpm and 7000 rpm particularly occurs for 25 and 30% PS/copolymer blends. The 4000 rpm and 5500 rpm data shows the advantage trails off for 35% PS blends.

Claim 1 recites 25 to 35 % PS. Claims 6, 7, 9 and 10 recite narrower percent

composition ranges to further be commensurate with the data and distinguish over the references.

At page 4, in discussing Claims 4 and 5, the Office action asserted sterilization with gamma radiation does not change the composition of the tube. It is respectfully submitted this is an oversimplification. Radiation can change and degrade materials as explained in the attached journal articles (ATTACHMENT II, *X-ray Radiation Damage Effects in Ps/Pbd Polymer Mixtures*, Teamour Nurushev, Eric Dufresne, and Steven B. Dierker Department of Physics, University of Michigan, Ann Arbor, MI, www.aps.anl.gov/xfd/communicator/user2000/nurushevt1.pdf; and ATTACHMENT III, *Radiation Sterilization - Polymer Materials Selection for Radiation Sterilized Products*, K.J. Hemmerich, Medical Device & Diagnostic Industry Magazine (Feb. 2000)). Radiation sterilization is common in the medical device industry. Thus, ability to withstand radiation is a significant property.

Data at page 7 of the present application shows, a blend of 30% PS / 70% S-Bu has better resistance to leakage after being subjected to radiation sterilization than pure S-Bu.

Also, data at page 7 of the present application shows, a blend of 30% PS / 70% S-Bu has better resistance to leakage after aging than pure S-Bu.

As explained above, it was unexpected that adding polystyrene to styrene butadiene would improve resistance to leakage because pure polystyrene (PS) was conventionally thought to be more brittle than pure styrene butadiene (S-Bu) copolymer as explained at page 1, third paragraph, of the present specification.

Claims 6, 7, 9 and 10 recite narrower percent composition ranges to further be commensurate with the data and distinguish over the references.

Thus, it is respectfully submitted these references neither alone nor combined make the

present invention obvious.

III. 35 USC 103 - Claim 8

Claim 8 stands are rejected as unpatentable over the references as applied to Claim 1, and further in view of Metcoff (US Pat. No. 4,818,516). It is respectfully submitted that Metcoff does not make up for the deficiencies of the references applied against its base Claim 1.

IV. Allowable Subject Matter

Applicants thank the Examiner for the indication that Claims 11-13 are allowable.

V. Conclusion

In view of the above, it is respectfully submitted that all objections and rejections are overcome. Thus, a Notice of Allowance is respectfully requested.

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ATTACHMENT I

MPEP 716.02(e)

FENAC:diphenyl ether ratio of 1:1 to 4:1 for the three specific ethers tested. For two of the claimed ethers, unexpected results were demonstrated over a ratio of 16:1 to 2:1, and the effectiveness increased as the ratio approached the untested region of the claimed range. The court held these tests were commensurate in scope with the claims and supported the nonobviousness thereof. However, for a third ether, data was only provided over the range of 1:1 to 2:1 where the effectiveness decreased to the "expected level" as it approached the untested region. This evidence was not sufficient to overcome the obviousness rejection.); *In re Lindner*, 457 F.2d 506, 509, 173 USPQ 356, 359 (CCPA 1972) (Evidence of nonobviousness consisted of comparing a single composition within the broad scope of the claims with the prior art. The court did not find the evidence sufficient to rebut the *prima facie* case of obviousness because there was "no adequate basis for reasonably concluding that the great number and variety of compositions included in the claims would behave in the same manner as the tested composition.").

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II. < DEMONSTRATING CRITICALITY OF A CLAIMED RANGE

To establish unexpected results over a claimed range, applicants should compare a sufficient number of tests both inside and outside the claimed range to show the criticality of the claimed range. *In re Hill*, 284 F.2d 955, 128 USPQ 197 (CCPA 1960).

716.02(e) Comparison With Closest Prior Art [R-2]

An affidavit or declaration under 37 CFR 1.132 must compare the claimed subject matter with the closest prior art to be effective to rebut a *prima facie* case of obviousness. *In re Burckel*, 592 F.2d 1175, 201 USPQ 67 (CCPA 1979). "A comparison of the claimed invention with the disclosure of each cited reference to determine the number of claim limitations in common with each reference, bearing in mind the relative importance of particular limitations, will usually yield the closest single prior art reference." *In re Merchant*, 575 F.2d 865, 868, 197 USPQ 785, 787 (CCPA 1978) (emphasis in original). Where the comparison is not identical with the reference disclosure, deviations therefrom should be explained, *In re*

Finley, 174 F.2d 130, 81 USPQ 383 (CCPA 1949), and if not explained should be noted and evaluated, and if significant, explanation should be required. *In re Armstrong*, 280 F.2d 132, 126 USPQ 281 (CCPA 1960) (deviations from example were inconsequential).

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I. < THE CLAIMED INVENTION MAY BE COMPARED WITH PRIOR ART THAT IS CLOSER THAN THAT APPLIED BY THE EXAMINER

Applicants may compare the claimed invention with prior art that is more closely related to the invention than the prior art relied upon by the examiner. *In re Holladay*, 584 F.2d 384, 199 USPQ 516 (CCPA 1978); *Ex parte Humber*, 217 USPQ 265 (Bd. App. 1961) (Claims to a 13-chloro substituted compound were rejected as obvious over nonchlorinated analogs of the claimed compound. Evidence showing unexpected results for the claimed compound as compared with the 9-, 12-, and 14- chloro derivatives of the compound rebutted the *prima facie* case of obviousness because the compounds compared against were closer to the claimed invention than the prior art relied upon.).

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II. < COMPARISONS WHEN THERE ARE TWO EQUALLY CLOSE PRIOR ART REFERENCES

Showing unexpected results over one of two equally close prior art references will not rebut *prima facie* obviousness unless the teachings of the prior art references are sufficiently similar to each other that the testing of one showing unexpected results would provide the same information as to the other. *In re Johnson*, 747 F.2d 1456, 1461, 223 USPQ 1260, 1264 (Fed. Cir. 1984) (Claimed compounds differed from the prior art either by the presence of a trifluoromethyl group instead of a chloride radical, or by the presence of an unsaturated ester group instead of a saturated ester group. Although applicant compared the claimed invention with the prior art compound containing a chloride radical, the court found this evidence insufficient to rebut the *prima facie* case of obviousness because the evidence did not show rela-

tive effectiveness over all compounds of the closest prior art. An applicant does not have to test all the compounds taught by each reference, “[h]owever, where an applicant tests less than all cited compounds, *the test must be sufficient to permit a conclusion respecting the relative effectiveness of applicant’s claimed compounds and the compounds of the closest prior art.*” *Id.* (quoting *In re Payne*, 606 F.2d 303, 316, 203 USPQ 245, 256 (CCPA 1979)) (emphasis in original).)

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III. < THE CLAIMED INVENTION MAY BE COMPARED WITH THE CLOSEST SUBJECT MATTER THAT EXISTS IN THE PRIOR ART

Although evidence of unexpected results must compare the claimed invention with the closest prior art, applicant is not required to compare the claimed invention with subject matter that does not exist in the prior art. *In re Geiger*, 815 F.2d 686, 689, 2 USPQ2d 1276, 1279 (Fed. Cir. 1987) (Newman, J., concurring) (Evidence rebutted *prima facie* case by comparing claimed invention with the most relevant prior art. Note that the majority held the Office failed to establish a *prima facie* case of obviousness.); *In re Chapman*, 357 F.2d 418, 148 USPQ 711 (CCPA 1966) (Requiring applicant to compare claimed invention with polymer suggested by the combination of references relied upon in the rejection of the claimed invention under 35 U.S.C. 103 “would be requiring comparison of the results of the invention with the results of the invention.” 357 F.2d at 422, 148 USPQ at 714.).

716.02(f) Advantages Disclosed or Inherent

The totality of the record must be considered when determining whether a claimed invention would have been obvious to one of ordinary skill in the art at the time the invention was made. Therefore, evidence and arguments directed to advantages not disclosed in the specification cannot be disregarded. *In re Chu*, 66 F.3d 292, 298-99, 36 USPQ2d 1089, 1094-95

(Fed. Cir. 1995) (Although the purported advantage of placement of a selective catalytic reduction catalyst in the bag retainer of an apparatus for controlling emissions was not disclosed in the specification, evidence and arguments rebutting the conclusion that such placement was a matter of “design choice” should have been considered as part of the totality of the record. “We have found no cases supporting the position that a patent applicant’s evidence or arguments traversing a § 103 rejection must be contained within the specification. There is no logical support for such a proposition as well, given that obviousness is determined by the totality of the record including, in some instances most significantly, the evidence and arguments proffered during the give-and-take of *ex parte* patent prosecution.” 66 F.3d at 299, 36 USPQ2d at 1095.). See also *In re Zenitz*, 333 F.2d 924, 928, 142 USPQ 158, 161 (CCPA 1964) (evidence that claimed compound minimized side effects of hypotensive activity must be considered because this undisclosed property would inherently flow from disclosed use as tranquilizer); *Ex parte Sasajima*, 212 USPQ 103, 104 - 05 (Bd. App. 1981) (evidence relating to initially undisclosed relative toxicity of claimed pharmaceutical compound must be considered).

The specification need not disclose proportions or values as critical for applicants to present evidence showing the proportions or values to be critical. *In re Saunders*, 444 F.2d 599, 607, 170 USPQ 213, 220 (CCPA 1971).

716.02(g) Declaration or Affidavit Form

“The reason for requiring evidence in declaration or affidavit form is to obtain the assurances that any statements or representations made are correct, as provided by 35 U.S.C. 25 and 18 U.S.C. 1001.” Permitting a publication to substitute for expert testimony would circumvent the guarantees built into the statute. *Ex parte Gray*, 10 USPQ2d 1922, 1928 (Bd. Pat. App. & Inter. 1989). Publications may, however, be evidence of the facts in issue and should be considered to the extent that they are probative.

ATTACHMENT II

X-ray Radiation Damage Effects in Ps/Pbd Polymer Mixtures, Teamour Nurushev, Eric Dufresne, and Steven B. Dierker Department of Physics, University of Michigan, Ann Arbor, MI, www.aps.anl.gov/xfd/communicator/user2000/nurushevt1.pdf

X-ray Radiation Damage Effects in Ps/Pbd Polymer Mixtures

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Introduction

Soft condensed matter organic-based materials are often susceptible to various kinds of damage upon prolonged exposure to high energy radiation beams, such as electron, γ -ray, or x-ray beams. This can be an important issue in X-ray Photon Correlation Spectroscopy (XPCS) studies of the dynamics of such materials. Often the effects of radiation damage are cumulative over time. This implies that there may be a maximum duration for an XPCS measurement at a particular position in a material. Very little information for x-ray radiation effects on organic materials exists in a form which can be directly useful in determining this maximum duration for an XPCS experiment. In this report, we describe such results for a polymer mixture of Polystyrene and Polybutadiene.

In XPCS experiments, one measures the low frequency dynamics of a material by determining the time autocorrelation function of the fluctuations in the speckle pattern, which modulates the scattering from the materials.[1] Speckle occurs when the sample is illuminated with a coherent x-ray beam. Transversely coherent x-ray beams are prepared by collimating the x-rays with an aperture whose dimensions are comparable to the transverse coherence lengths of the x-rays. At a typical beamline at the APS, the transverse coherence lengths, l_{\perp} , are $\sim 5 \mu\text{m}$ in the horizontal and $30 \mu\text{m}$ in the vertical. The flux through this area is determined by the brightness of the source and the degree to which the beam is monochromatized. The longitudinal coherence length, l_{\parallel} , is inversely proportional to the monochromaticity of the x-ray beam. The two most common arrangements are to either use the natural bandwidth of the undulator ($\Delta E/E \sim 2.5\%$), a so-called 'pink' beam with l_{\parallel} of order 50 \AA , or that of either a Ge or Si monochromator, with l_{\parallel} of order $1 \mu\text{m}$. Although l_{\parallel} is rather small for a pink beam, it is nonetheless sufficient for coherent small angle x-ray scattering (SAXS) measurements. On the MHATT-CAT Sector 7 ID line, we typically produce coherent fluxes for XPCS experiments of $\sim 4 \times 10^8 \text{ ph/sec}/(5 \mu\text{m})^2$ with Ge resolution and $\sim 4 \times 10^{10} \text{ ph/sec}/(5 \mu\text{m})^2$ with a pink beam. Although these fluxes are not particularly large, they correspond to quite high intensities. As a result, they are capable of producing significant damage in organic materials.

In this report, we describe the effects of exposure of a polymer mixture, Polystyrene/Polybutadiene, to x-rays. We find that the SAXS changes dramatically upon irradiation and that the changes scale with radiation dose for widely varying dose rates. There also appears to be a threshold dose, below which no significant effects of damage are observable in the SAXS pattern.

Methods and Materials

This experiment was performed on the undulator beamline at sector 7 of the Advanced Photon Source, operated by MHATT-CAT. With the undulator fundamental set at 9.0 keV , the white beam was collimated with white beam slits to $100 \mu\text{m}$

by $100 \mu\text{m}$. In the experimental hutch 35 m from the source, two small Pt coated mirrors were used to produce a 'pink beam'. The doubly reflected beam had a bandpass of $\Delta E/E = 2.55\%$. The samples were illuminated with two different size x-ray beams, $(5 \mu\text{m})^2$ and $(50 \mu\text{m})^2$, with fluxes of $4 \times 10^{10} \text{ ph/sec}$ and $5 \times 10^{12} \text{ ph/sec}$, respectively, to check for any dependence on beam size. Attenuators were used to vary the incident flux for each beam size in order to check for any dependence on dose rate. The polymer studied was a 65% by weight mixture of 1000 MW polystyrene with 2000 MW polybutadiene. This mixture has an upper critical solution temperature of $\sim 34^\circ \text{C}$. Measurements were made for sample temperatures ranging from 80°C to 25°C , i.e., both above and below T_c . Time resolved SAXS patterns from the mixture were measured with a direct detection CCD camera as a function of time after the start of x-ray exposure.

Results

Fig. 1 shows the time dependence of the measured SAXS scattering rate a sample illuminated by an attenuated $(50 \mu\text{m})^2$ pink beam at a sample temperature of 40°C . At the earliest times, the SAXS is time invariant and is due to scattering from composition fluctuations in this critical mixture. This temperature dependent critical scattering will be reported separately. This initial 'quiescent' period is followed by a strong increase in scattering at wavevectors below $\sim 0.025 \text{ \AA}^{-1}$. Finally, in the late time behavior the scattering curve uniformly becomes smaller. We believe the initial increase in scattering at small wavevectors is due to the x-ray radiation induced formation of large cross-linked molecules. The eventual diminution of the scattering at late times is thought to be due to the growth in size of the cross-linked molecules, with their scattering moving to lower q , together with the reduction in scattering from composition fluctuations as the damaged material grows to fill the scattering volume being probed.

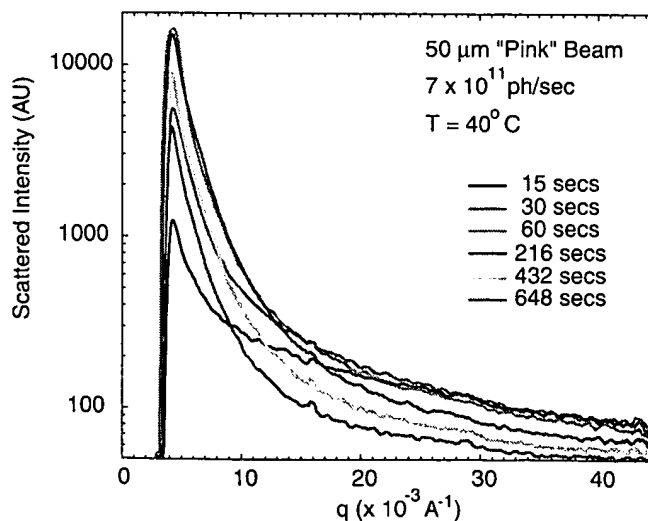


Figure 1. Time dependence SAXS from a Ps/Pbd mixture.

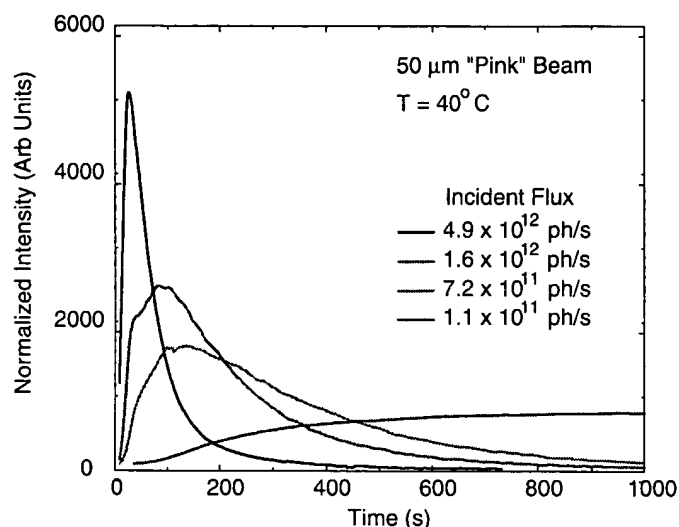


Figure 2. Time dependence of the scattering from the mixture at $q = 6.5 \times 10^{-3} \text{ \AA}^{-1}$ and a temperature of 40°C for various incident x-ray fluxes.

In Figure 2, the time dependence of the scattering rate at a wavevector of $q = 6.5 \times 10^{-3} \text{ \AA}^{-1}$ and a sample temperature of 40°C is shown for various incident fluxes obtained from a $(50 \text{ } \mu\text{m})^2$ pink beam by the use of attenuators. Again, we see three phases to the time dependence: a very early time-independent phase followed by an intermediate phase with a strong rise in scattering and a late phase with a strong decrease in scattering.

The large variation in times for the three phases in Figure 2 for different incident fluxes, with lower fluxes taking longer times to develop, suggests that the sample damage may be a function of accumulated dose. This relation is shown to be obeyed remarkably well in Figure 3, where the scattering intensity is normalized to 1 at its maximum and plotted versus radiation dose, expressed in kGy. The data follow a very similar curve

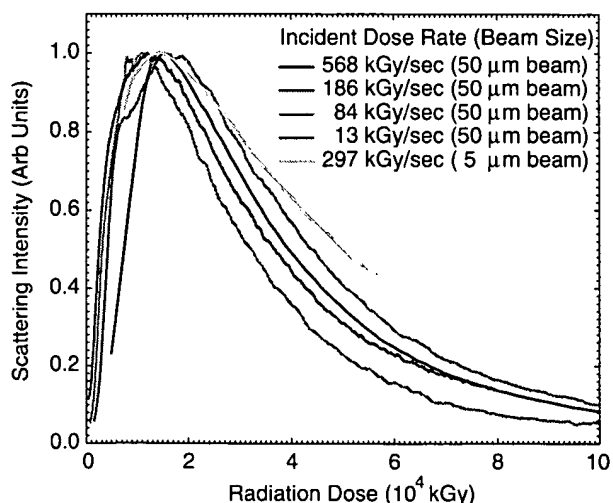


Figure 3. Scaling of the SAXS at $q = 6.5 \times 10^{-3} \text{ \AA}^{-1}$ with accumulated radiation dose, for various incident dose rates.

even though the dose rate varies by a factor of 43 and the incident beam size varies from $(5 \text{ } \mu\text{m})^2$ to $(50 \text{ } \mu\text{m})^2$.

Discussion

The results in Figure 1-3 show that x-ray radiation induced damage to this polymer mixture depends on accumulated dose and can result in dramatic changes in the polymer structure on relatively short time scales. Analysis of the data indicate that the first phase of irradiation, during which the structure and scattering are essentially unaffected by the irradiation lasts up to about 2000 kGy. This damage threshold can be used to estimate the approximate maximum duration of an XPCS experiment on this material for different incident coherent x-ray intensities. A pink beam with a flux of $4 \times 10^{10} \text{ ph/s}/(5 \text{ } \mu\text{m})^2$ results in a deposited dose rate of 180 kGy/sec. At this dose rate, the damage threshold dose would be reached in only 10 seconds. With a Ge resolution x-ray beam, the dose rate is lowered to 1.8 kGy/sec and the time to damage threshold increases to ~ 1000 seconds. In these mixtures, the relaxation time for concentration fluctuations can be as long as 1000 seconds. Thus, Ge resolution coherent beams are necessary. In addition, although the maximum measurement duration is of the order of the slowest relaxation time, ensemble averaging techniques utilizing a CCD detector are capable of determining the autocorrelation functions under those conditions. XPCS measurements of the temperature and wavevector dependence of critical dynamics of this mixture will be reported separately.

The damage threshold reported here for the Ps/Pbd mixture will surely vary for different materials, depending on their chemistry and viscosity. For example, in a recent XPCS study[2] of concentration fluctuations in the binary fluid mixture hexane/nitrobenzene, no observable radiation damage effects were observed even for much larger doses than the maximum doses studied here. This is likely due to a combination of the small molecules being more resistant to damage and the mixture having a very low viscosity, which allows any defect that are produced to diffuse out of the volume probed by the x-ray in much less than 1 second.

Finally, these results have implications for future experiments at a 4th generation x-ray sources, where the average brightness is expected to be several orders of magnitude greater than for the APS. Such large increases in dose rate at a 4th generation source may limit the ability to study *slow* fluctuations in many organic materials. On the other hand, such a large increase in flux would make it possible to study much faster fluctuations, which could be studied before the sample is destroyed.

Acknowledgments

Work supported in part by DoE grant DE-FG02-99ER45743. Use of the Advanced Photon Source was supported by the U.S. Department of Energy, Basic Energy Sciences, Office of Science, under Contract No. W-31-109-Eng-38.

References

- [1] For a recent reference, see A. Malik, et. al. Phys. Rev. Lett. **81**, 5832 (1998), and references therein.
- [2] E. Dufresne, T. Nurushev, R. Clarke, S. Dierker, to be published.

ATTACHMENT III

Radiation Sterilization - Polymer Materials Selection for Radiation Sterilized Products, K.J. Hemmerich, Medical Device & Diagnostic Industry Magazine (Feb. 2000)



Medical Device & Diagnostic Industry Magazine
MDDI Article Index

Originally Published February 2000

RADIATION STERILIZATION

Polymer Materials Selection for Radiation-Sterilized Products

Choosing the right polymer for a radiation-sterilized device requires an understanding of radiation effects, manufacturing processes, and the product's intended use.

Karl J. Hemmerich

Gamma and electron-beam irradiation are among the most popular and well established processes for sterilizing polymer-based medical devices. It has been long known, however, that these techniques can lead to significant alterations in the materials being treated. High-energy radiation produces ionization and excitation in polymer molecules. These energy-rich species undergo dissociation, abstraction, and addition reactions in a sequence leading to chemical stability. The stabilization process—which occurs during, immediately after, or even days, weeks, or months after irradiation—often results in physical and chemical cross-linking or chain scission. Resultant physical changes can include embrittlement, discoloration, odor generation, stiffening, softening, enhancement or reduction of chemical resistance, and an increase or decrease in melt temperature. This article discusses how and why irradiated polymeric materials change,



presents data on the radiation stability of various polymers, and offers some general guidelines for material selection.

Ionizing radiation is a unique and powerful means of modifying polymers, particularly since the changes occur when materials are in a solid state, as opposed to chemical or thermal reactions carried out in hot or melted polymers. While solid-state modification may have significant advantages, any changes in material characteristics or performance brought about by radiation are governed by structure/property relationships that are perfectly analogous to those generated by other chemical and thermal processes. These include polymerization, grafting, cross-linking, changes in saturation, chain scission (degradation), oxidation, cyclization, isomerization, amorphization, and crystallization.

Many important physical or chemical properties of polymers can be modified with radiation. Among these are molecular weight, chain length, entanglement, polydispersity, branching, pendant functionality, and chain termination. Understanding how and to what extent these characteristics can be altered as a function of the level of radiation exposure (dose) is crucial to predicting the performance and utility of irradiated plastics.

The influence of radiation on the properties and performance of a polymer differs according to whether the material degrades or cross-links, and this in turn depends on specific sensitivities or susceptibilities inherent in the polymer backbone. All materials have been found to break down at very high radiation doses; however, the range of doses under which a given plastic will maintain its desirable properties depends greatly on the chemical structure of the polymer. Indeed, below the destructive level of exposure, radiation treatment can impart many benefits and enhance properties of commercial value. By gaining sufficient knowledge about these beneficial radiation-induced effects, device manufacturers can make thoughtful choices regarding polymers used in sterile medical products and ensure that critical elements of material and product performance are not compromised.

RADIATION EFFECTS

Because the effects of ionizing radiation depend greatly on polymer chemical structure, the dose necessary to produce similar significant effects in two different materials can vary

from values as low as 4 kGy in polytetrafluoroethylene to 4000 kGy or more in styrene or polyimide. Even the lowest doses, however, can engender significant alterations. For example, in a typical polyethylene with an average molecular weight of about 100,000 and readily soluble in a solvent such as Decalin, only one cross-link per 14,000 monomer (ethylene) units can cause gelation (insolubility).

Radiation effects on the properties of a polymer can also be difficult to predict, especially in the presence of certain additives that can help to prevent radiation damage to plastics. These compounds are frequently termed "antirads," and generally are substances that also act as antioxidants. They function either as reactants, combining readily with radiation-generated free radicals in the polymer, or as primary energy absorbers, preventing the radiation's interaction with the polymer itself.

Radiation normally affects polymers in two basic manners, both resulting from excitation or ionization of atoms. The two mechanisms are chain scission, a random rupturing of bonds, which reduces the molecular weight (i.e., strength) of the polymer, and cross-linking of polymer molecules, which results in the formation of large three-dimensional molecular networks.

Most often, both of these mechanisms occur as polymeric materials are subjected to ionizing radiation, but frequently one mechanism predominates within a specific polymer. As a result of chain scission, very-low-molecular-weight fragments, gas evolution, and unsaturated bonds may appear. Cross-linking generally results in an initial increase in tensile strength, while impact strength decreases and the polymer becomes more brittle with increased dose.

For polymers with carbon-carbon chains (backbones), it has been observed that cross-linking generally will occur if the carbons have one or more hydrogen atoms attached, whereas scission occurs at tetra-substituted carbons. Polymers containing aromatic molecules generally are much more resistant to radiation degradation than are aliphatic polymers; this is true whether or not the aromatic group is directly in the chain backbone or not. Thus, both polystyrenes, with a pendant aromatic group, and polyimides, with an aromatic group directly in the polymer backbone, are relatively resistant to high doses (>4000 kGy).

From a product use standpoint, the loss of mechanical properties is the most important characteristic effected by irradiation of polymers. These properties include tensile strength, elastic modulus, impact strength, shear strength, and elongation. Embrittlement may occur even as irradiated polymers decrease in hardness. Crystallinity and, hence, density characteristics may also change as chain scission continues.

When a polymer is subjected to irradiation by ionizing radiation—such as gamma rays, x-rays, or accelerated electrons—various effects can be expected from the ionizations that occur. The ratio of resultant recombination, cross-linking, and chain scission will vary from polymer to polymer and to some degree from part to part based on the chemical composition and morphology of the polymer, the total radiation dose absorbed, and the rate at which the dose was deposited. The ratio is also significantly affected by the residual stress processed into the part, the environment present during irradiation (especially the presence or absence of oxygen), and the postirradiation storage environment (temperature and oxygen).

EFFECTS OF OXYGEN AND DOSE RATE

The environmental conditions under which radiation processing is conducted can significantly affect the properties of the polymer material. For example, the presence of oxygen or air during irradiation produces free radicals that are often rapidly converted to peroxidic radicals. The fate of these radicals depends on the nature of the irradiated polymer, the presence of additives, and other parameters such as temperature, total dose, dose rate, and sample size. A variation in processing conditions in the presence of polymer additives can result in gas evolution and formation of other degradation products from these small molecules, with the possibility of producing irritants or other undesirable compounds.

A significant difference in irradiation processing exists between electron-beam and gamma sterilization related to dose rate and, ultimately, to the oxidation degradation of material at or near the surface. Dose rate refers to how fast energy is absorbed and depends on many factors including the source, strength, and size of the radiation field; its distance from the source; and the type of radiation. For

electron and gamma sources of the same strength, the dose rate of the electron source is many times greater than that of the gamma source. This is because the electron beam is unidirectional and is concentrated in a much smaller region, and because the interaction of electrons with other electrons is much stronger than with photons.

Although the difference may be minute, it can be said in an absolute sense that all polymeric materials undergo less material embrittlement in electron-beam than in gamma-ray sterilization as a result of reduced oxidative chain scission. For many products, this is not critical, but is important to keep in mind when selecting a radiation sterilization process for oxidation-sensitive materials such as polypropylene, nylon, or Teflon or for products containing thin profiles, such as films and fibers.

Additional explanation will help clarify this phenomenon. As a polymer is irradiated, radicals are formed in a concentration proportional to the local dose. However, the associated stabilizing chemical reactions that follow are proportional to the local concentrations of reactants. Because the concentration of reactants differs by location (i.e., higher oxygen near exterior surfaces), the resultant radio-chemical stabilizing reactions are thus heterogeneous.

In both gamma and electron-beam irradiation systems, available oxygen is quickly consumed within the polymer. However, in the case of electron-beam processing, the time of energy application is so short that before more oxygen can permeate into the material from its external surfaces, the application of radiant energy has been terminated, the direct formation of additional radicals ceases, and the stabilizing chemistry pursues alternate, less-degrading routes (recombination or cross-linking). In simple terms, the chemistry changes as a result of a starved chemical reaction—much as a fire goes out when the oxygen is consumed in a closed container. In gamma irradiation, the application of ionizing energy continues over a much longer period of time, allowing reactants, such as oxygen, to permeate back into depleted areas of the material, resulting in a greater degree of chain scission.

COLOR AND ODOR

A common undesirable effect resulting from the irradiation of some polymers is discoloration (usually yellowing) from the

development of specific chromophores or color centers in the polymer. Color development, which occurs at widely differing doses in various polymers, may diminish or increase with storage time after irradiation. Often, discoloration appears prior to any measurable loss in physical properties. Such as is the case, for example, with PVC, in which radiation-induced yellowing from conjugated double bonds develops at a dose much lower than is necessary to cause any reduction in the material's physical properties.

Another problematic effect in some polymers that results from specific radio-stabilizing chemistries is odor. The polymers that most commonly exhibit post-irradiation odor are polyethylene, PVC (rancid oil odor from oxidized soybean and linseed oils in the plasticizer), and polyurethane.

If the reaction chemistries causing the odors are understood they can often be mitigated through the use of antioxidants, different processing temperatures, or selection of a higher-molecular-weight polymer. Odor reduction can also be accomplished through the use of gas-permeable packaging (for example, Tyvek, paper) and elevated temperature conditioning.

MATERIAL SELECTION

In addition to personal experience, materials databases, supplier information, and literature searches can be used to help avoid potential problems with polymers that are less radiation resistant than required for a particular product's design and function. Material selection should be done with diligence, especially when dealing with thin sections such as films, coatings, and fibers as well as with materials having low radiation resistance such as acetal, polypropylene, or Teflon (these three polymers can be remembered as those that are "APT" to fail). It must be remembered that the physical properties of irradiated polymers are subject to significant variations due to residual or functional stress, section thickness, molecular weight, morphology, moisture, and storage environment (oxygen/temperature), and must be tested in the specific application under consideration.

The selection of materials for radiation sterilization should start with the following basic rules:

- Most medical plastics are durable in radiation.
- Use the highest-molecular-weight material (with the

narrowest molecular-weight distribution) that is possible for the application.

- Aromatic materials are more radiation resistant than are aliphatic materials.
- Amorphous materials are more radiation resistant than are semicrystalline materials.
- Higher levels of antioxidants improve radiation resistance.
- Low-density materials are more radiation resistant than high-density materials.
- Materials with small pendant (side) groups are more radiation resistant.
- For semicrystalline materials, the lower the crystallinity, the greater the radiation resistance.
- Materials with low oxygen permeability are more radiation resistant.
- Avoid materials that are "APT" to fail: acetal, polypropylene (unstabilized), or Teflon (PTFE).

Information derived from government, industrial, and scientific studies and publications concerning radiation effects on polymer properties after exposure to various doses is summarized in Figures 1 and 2, which graphically display the dose at which a number of common thermoplastics and thermosets experience a 25% loss in elongation. (Loss of elongation is a commonly used measure of the effect of irradiation.) These figures provide a visual means of making an initial estimate of a polymer's ability to withstand a typical sterilization dose (10–50 kGy) or a higher dose used in a more specialized radiation process. A more qualitative summary of the radiation stability of selected polymeric materials is provided in Table I.

CONCLUSION

When used to enhance polymer properties or to sterilize polymer-based medical products, ionizing radiation interacts with polymers via two primary mechanisms: chain scission to reduce molecular weight and cross-linking to generate large polymer networks. Both mechanisms occur in all polymers during irradiation, but one generally dominates. Polymers vary in sensitivity to radiation from PTFE and polyacetal, with damage occurring at doses as low as 4 kGy, to polystyrenes, polyimides, and LCP, which can tolerate doses as high as 105 kGy without significant damage.

Polymers containing aromatic groups have much greater resistance to radiation damage than those with aliphatic structure. Most thermoplastics, essentially all thermosets, and most elastomers can withstand at least one radiation sterilization (<50 kGy) without significant damage. Because of oxidative effects, polymeric materials used in adhesives, fibers, films, and encapsulates show slightly lower radiation tolerance compared with bulk polymers; however, the use of antioxidant additives can significantly offset the effects of radiation.

With a basic understanding of the effects of radiation on polymers, reference data available from polymer manufacturers and other sources, and a thorough understanding of the product's manufacturing process and intended use, wise choices of radiation-tolerant materials can be made for the majority of medical product applications.

REFERENCES

1. Information sources include polymer manufacturers' data; "Effects of Radiation on Polymers & Elastomers," NASA/Jet Propulsion Laboratories, 1988; Skeins and Williams, "Ionizing Radiation Effect on Selected Biomedical Polymers"; Kiang, "Effect of Gamma Irradiation on Elastomeric Closures," Technical report 16, PDA, 1992; Ley, "The Effects of Irradiation on Packaging Materials," 1976.

2. Some information derived from IAEA, 1990.

Karl J. Hemmerich is general manager and corporate technical advisor at Isomedix Corp.'s gamma irradiation facility located in Sandy, UT. He was formerly president of Ageless Processing Technologies, a consulting firm specializing in the medical disposables market, and has also worked at Ivac Corp., Cutter Laboratories, and Becton Dickinson. He was a member of the task force that developed the technical information report for postirradiation of materials (ISO 11137).

Photo by Roni Ramos

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Interview Summary

Application No.

10/051,608

Applicant(s)

MCCANN ET AL.

Examiner

Thao T. Tran

Art Unit

1711

All participants (applicant, applicant's representative, PTO personnel):

(1) Thao T. Tran.

(3) _____.

(2) Anthony Venturino.

(4) _____.

Date of Interview: 15 September 2004.

Type: a) ☐ Telephonic b) ☐ Video Conference

c) ☒ Personal [copy given to: 1) ☐ applicant 2) ☒ applicant's representative]

Exhibit shown or demonstration conducted: d) ☐ Yes e) ☒ No.

If Yes, brief description: _____.

Claim(s) discussed: 1-13.

Identification of prior art discussed: JP '190, Okuda et al. and Blackwelder et al.

Agreement with respect to the claims f) ☐ was reached. g) ☐ was not reached. h) ☒ N/A.

Substance of Interview including description of the general nature of what was agreed to if an agreement was reached, or any other comments: See Continuation Sheet.

(A fuller description, if necessary, and a copy of the amendments which the examiner agreed would render the claims allowable, if available, must be attached. Also, where no copy of the amendments that would render the claims allowable is available, a summary thereof must be attached.)

THE FORMAL WRITTEN REPLY TO THE LAST OFFICE ACTION MUST INCLUDE THE SUBSTANCE OF THE INTERVIEW. (See MPEP Section 713.04). If a reply to the last Office action has already been filed, APPLICANT IS GIVEN ONE MONTH FROM THIS INTERVIEW DATE, OR THE MAILING DATE OF THIS INTERVIEW SUMMARY FORM, WHICHEVER IS LATER, TO FILE A STATEMENT OF THE SUBSTANCE OF THE INTERVIEW. See Summary of Record of Interview requirements on reverse side or on attached sheet.

Examiner Note: You must sign this form unless it is an Attachment to a signed Office action.

Thao Tran
Examiner's signature, if required

Continuation of Substance of Interview including description of the general nature of what was agreed to if an agreement was reached, or any other comments: Applicants' representative pointed out that the presently claimed invention differs from the prior art in that the sidewalls and closed end of the tube as claimed comprises a blend of styrene-butadiene and 25-35% by weight of polystyrene, whereas Okuda and Blackwelder teach the composition used as heat shrinkable film and this would not lead one to use their compositions for the sidewalls and end of a medical tube. Applicants also asserted the examples in the application show unexpected results.

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